AMENDMENTS TO THE CLAIMS

Listing of the Claims

This listing replaces all prior versions and listings of claims in the application.

1.-62. (Canceled)

63. (Currently amended) [[~~An~~]] A monoclonal antibody or a functional fragment thereof, ~~which~~ that is a single substance without forming a polymer and that binds to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2, ~~R as a monomer~~ independently of exogenous factors other than the antibody and the functional fragment thereof.

64. (Currently amended) [[An]] A monoclonal antibody or a functional fragment thereof, ~~which binds~~ that is a single substance without forming a polymer and that binds to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2 ~~R as a monomer~~, independently of exogenous factors other than the antibody and the functional fragment thereof, and the survival rate of carcinoma cells in the following test using the said antibody or functional fragment thereof is 80% or less,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which were colon carcinoma cells, at a concentration of 1.0 x 10^5/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) the [[~~an~~]] antibody or the [[a]] functional fragment thereof which is bound to TRAIL-R2 [[~~R~~]] dissolved in RPMI-1640 medium containing 10% FCS such that a concentration of the antibody or the functional fragment thereof becomes 1000ng/ml when it is added to each well at 10μl/well, culturing each well at 37°C under 5.0% carbon dioxide gas for 48 hours, washing each well once with PBS and adding a fresh RPMI-1640 medium containing 10% FCS at100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQ_{UEOUS} Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is calculates using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing carcinoma cells and the antibody or the functional fragment thereof ~~tested~~, "b" represents the measured value of the absorbance of a carcinoma cell-free well, and "c" represents (i) the measured value of the absorbance of a well containing carcinoma cells and a control antibody which is not bound to carcinoma cells and is [[~~has~~]] the same subclass as [[~~with~~]] the antibody or the functional fragment thereof bound to TRAIL-R2 [[~~R~~]] when the antibody or the functional fragment thereof has a constant region, or (ii) the measured value of a well containing carcinoma cells and a control antibody which is not bound to the carcinoma cells and does not have a constant region when the antibody or the functional fragment thereof does not have a constant region).

65. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 64, wherein the survival rate is 60% or less.

66. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 64, wherein the survival rate is 40% or less.

67. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 64, wherein the survival rate is 20% or less.

68. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 64, wherein the survival rate is 10% or less.

69. (Currently amended) [[~~An~~]] A monoclonal antibody or a functional fragment thereof, which is a single substance without forming a polymer and which binds to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2 ~~R as a monomer~~, independently of exogenous factors other than the antibody and the functional fragment thereof, and the survival rate of carcinoma cells in the following test using the said antibody is 80% or less,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which were colon carcinoma cells, at a concentration of 1.0 x 10^5/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) [[~~an~~] the antibody or the functional fragment thereof which is bound to TRAIL-R2 [[~~R~~]] dissolved in RPMI-1640 medium containing 10% FCS such that a concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing each well at 37°C under 5.0% carbon dioxide gas for 48 hours, washing each well once with PBS and adding a fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQ$_{UEOUS}$ Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is calculates using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing carcinoma cells ~~tested~~, "b" represents the measured value of a carcinoma cell-free well, and "c" represents the measured value of a well containing carcinoma cells and a control antibody which is [[~~has~~]] the same subclass as [[~~with~~]] the antibody bound to TRAIL-R2 [[~~R~~]] and is not bound to the carcinoma cells).

70. (Currently Amended) [[~~An~~]] The monoclonal antibody or the functional fragment thereof of claim 69, wherein the survival rate is 60% or less.

71. (Currently Amended) [[~~An~~]] The monoclonal antibody or the functional fragment thereof of claim 69, wherein the survival rate is 40% or less.

72. (Currently Amended) [[~~An~~]] The monoclonal antibody or the functional fragment thereof of claim 69, wherein the survival rate is 20% or less.

73. (Currently Amended) [[~~An~~]] The monoclonal antibody or the functional fragment thereof of claim 69, wherein the survival rate is 10% or less.

74. (Currently amended) [[~~An~~]] A monoclonal antibody or a functional fragment thereof which is a single substance without forming a polymer, binding ~~which binds~~ to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2 ~~R as a monomer~~, independently of exogenous factors other than the antibody and the functional fragment thereof, and the survival rate of carcinoma cells in the following test using the said antibody is 80% or less,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which were colon carcinoma cells, at a concentration of 5 x 10^4/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) [[~~an~~]] the antibody or the functional fragment thereof which is bound to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that a concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing at 37°C under 5.0% carbon dioxide gas for 1 hour, adding a control antibody which is [[~~has~~]] the same subclass as [[~~with~~]] the antibody bound to TRAIL-R2 and is not bound to carcinoma cells such that a concentration is 100μg/ml, adding goat anti-human IgG (γ)-specific polyclonal antibodies at a final concentration of 10μg/ml, culturing each well at 37°C under 5.0% carbon dioxide gas for 2 days, washing each well once with PBS and adding a fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQ_{UEOUS} Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is calculates using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing carcinoma cells tested, "b" represents the measured value of a carcinoma cell-free well, and "c" represents the measured value of a well containing carcinoma cells and a control antibody which [[~~has~~]] is the same subclass [[~~with~~]] as the antibody bound to TRAIL-R2 and is not bound to the carcinoma cells).

75. (Currently amended) [[~~An~~]] ~~The monoclonal~~ antibody or the functional fragment thereof of claim 74, wherein the survival rate is 60% or less.

76. (Currently amended) [[~~An~~]] ~~The monoclonal~~ antibody or the functional fragment thereof of claim 74, wherein the survival rate is 40% or less.

77. T (Currently amended) [[~~An~~]] ~~The monoclonal~~ antibody or the functional fragment thereof of claim 74, wherein the survival rate is 20% or less.

78. (Currently amended) [[~~An~~]] ~~The monoclonal~~ antibody or the functional fragment thereof of claim 74, wherein the survival rate is 10% or less.

79. (Currently amended) [[~~An~~]] A monoclonal antibody or a functional fragment thereof which is a single substance without forming a polymer, binding to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2 ~~R as a monomer~~, independently of exogenous factors other than the antibody and the functional fragment thereof, and the survival rate of carcinoma cells in the following test using the said antibody is 80% or less,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which were colon carcinoma cells, at a concentration of 5 x 10^4/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) [[~~an~~]] the antibody or the functional fragment thereof which is bound to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that a concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing at 37°C under 5.0% carbon dioxide gas for 1 hour, adding a control antibody which [[~~has~~]] is the same subclass [[~~with~~]] as the antibody bound to TRAIL-R2 and is not bound to carcinoma cell such that a concentration is 3μg/ml, adding goat anti-human IgG (γ)-specific polyclonal antibodies at a final concentration of 10μg/ml, culturing

each well at 37°C under 5.0% carbon dioxide gas for 2 days, washing each well once with PBS and adding a fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQ_{UEOUS} Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is calculates using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing carcinoma cells ~~tested~~, "b" represents the measured value of a carcinoma cell-free well, and "c" represents the measured value of a well containing carcinoma cells and a control antibody which [[~~has~~]] is the same subclass [[with]] as the antibody bound to TRAIL-R2 and is not bound to the carcinoma cells).

80. (Currently amended) [[~~An~~]] The monoclonal antibody or the functional fragment thereof of claim 79, wherein the survival rate is 60% or less.

81. (Currently amended) [[~~An~~]] The monoclonal antibody or the functional fragment thereof of claim 79, wherein the survival rate is 40% or less.

82. (Currently amended) [[~~An~~]] The monoclonal antibody or the functional fragment thereof of claim 79, wherein the survival rate is 20% or less.

83. (Currently amended) [[~~An~~]] The monoclonal antibody or the functional fragment thereof of claim 79, wherein the survival rate is 10% or less.

84. (Currently amended) [[~~An~~]] A monoclonal antibody or a functional fragment thereof, which is a single substance without forming a polymer, binding to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2 ~~R as a monomer~~, independently of exogenous factors other than the antibody and the functional fragment thereof, and the survival rate of carcinoma cells is 80% or less on condition that (1)1.0 x 10^5/ml of carcinoma cells and (2)1000ng/ml of the antibody or the functional fragment thereof are cultured at 37°C under 5.0% carbon dioxide gas for 48 hours ~~is 80% or less~~.

85. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 84, wherein the survival rate is 60% or less.

86. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 84, wherein the survival rate is 40% or less.

87. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 84, wherein the survival rate is 20% or less.

88. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 84, wherein the survival rate is 10% or less.

89. (Currently amended) [[~~An~~]] A monoclonal antibody or a functional fragment thereof, which is a single substance without forming a polymer and which binds to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2 ~~as a monomer~~ independently of exogenous factors other than the antibody and the functional fragment thereof, and the survival rate of carcinoma cells is 80% or less on condition that (1)5 x 10^4/ml of carcinoma cells, (2)1000ng/ml of the antibody, (3)100μg/ml of a control antibody or a functional fragment thereof which is [[~~has~~]] the same subclass [[~~with~~]] as the antibody or the functional fragment thereof bound to TRAIL-R2 and is not bound to carcinoma cells and (4)an antibody which binds to both the antibody or the functional fragment thereof bound to TRAIL-R2 and the control antibody are cultured at 37°C under 5.0% carbon dioxide gas for 48 hours ~~is 80% or less~~.

90. (Currently amended) [[An]] The monoclonal antibody or [[a]] the functional fragment thereof of claim 89, wherein the survival rate is 60% or less.

91. (Currently amended) [[An]] The monoclonal antibody or [[a]] the functional fragment thereof of claim 89, wherein the survival rate is 40% or less.

92. (Currently amended) [[An]] The monoclonal antibody or [[a]] the functional fragment thereof of claim 89, wherein the survival rate is 20% or less.

93. (Currently amended) [[An]] The monoclonal antibody or [[a]] the functional fragment thereof of claim 89, wherein the survival rate is 10% or less.

94. (Currently amended) [[~~An~~]] A monoclonal antibody or a functional fragment thereof, which is a single substance without forming a polymer, binding to ~~which binds to~~

TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2 ~~R as a monomer~~, independently of exogenous factors other than the antibody and the functional fragment thereof, and the survival rate of carcinoma cells is 80% or less on condition that (1)5 x 10^4/ml of carcinoma cells, (2)1000ng/ml of the antibody, (3)3μg/ml of a control antibody or a functional fragment thereof which [[~~has~~]] is the same subclass [[~~with~~]] as the antibody or the functional fragment thereof bound to TRAIL-R2 and is not bound to carcinoma cells and (4)an antibody which binds to both the antibody or the functional fragment thereof bound to TRAIL-R2 and the control antibody are cultured at 37°C under 5.0% carbon dioxide gas for 48 hours ~~is 80% or less~~.

95. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 94, wherein the survival rate is 60% or less.

96. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 94, wherein the survival rate is 40% or less.

97. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 94, wherein the survival rate is 20% or less.

98. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the unctional fragment thereof of claim 94, wherein the survival rate is 10% or less.

99. (Currently amended) [[~~An~~]] The monoclonal antibody or [[~~a~~]] the functional fragment thereof of claim 94, wherein the carcinoma cell is Colo205.

100. (Currently amended) An antibody or a functional fragment thereof which is a single substance without forming a polymer, binding ~~which is bound~~ to TRAIL-R2, the activity of inducing ~~to induce~~ apoptosis of which the antibody or [[~~a~~]] the functional fragment thereof on carcinoma cells expressing TRAIL-R2 does not substantially change depending on the presence or absence of an antibody which is bound to a constant region of the said antibody or the functional fragment thereof which is bound to TRAIL-R2.

101. (Currently amended) An antibody or a functional fragment thereof which is a single substance without forming a polymer, binding ~~which is bound~~ to TRAIL-R2, wherein the survival rate of carcinoma cells expressing TRAIL-R2 does not substantially change depending on the presence or absence of an antibody which is bound to a constant region of the said antibody or the functional fragment thereof which is bound to TRAIL-R2.

102. (Currently amended) A therapeutic composition, comprising as an active ingredient the antibody or the functional fragment thereof of claim 63 ~~any one of claims 63 to 101~~.

103. (Currently amended) A prophylactic or therapeutic agent against tumors, comprising as an active ingredient the antibody or the functional fragment thereof of claim 63 ~~any one of claims 63 to 101~~.

104. (Currently amended) [[A]] The prophylactic or therapeutic agent against tumors of claim 103, wherein the tumor is any one tumor selected from the group consisting of colon cancer, colorectal cancer, lung cancer, breast cancer, brain tumor, malignant melanoma, renal cell carcinoma, bladder cancer, leukemia, lymphomas, T cell lymphomas, multiple myeloma, gastric cancer, pancreas cancer, cervical cancer, endometrial carcinoma, ovarian cancer, esophageal cancer, liver cancer, head and neck squamous cell carcinoma, cutaneous cancer, urinary tract carcinoma, prostate cancer, choriocarcinoma, pharyngeal cancer, laryngeal cancer, thecomatosis, androblastoma, endometrium hyperplasy, endometriosis, embryoma, fibrosarcoma, Kaposi's sarcoma, hemangioma, cavernous hemangioma, angioblastoma, retinoblastoma, astrocytoma, neurofibroma, oligodendroglioma, medulloblastoma, ganglioneuroblastoma, glioma, rhabdomyosarcoma, hamartoblastoma, osteogenic sarcoma, leiomyosarcoma, thyroid sarcoma, and Wilms tumor ~~and the like~~.

105.-107. (Canceled)

108. (Currently amended) A method of producing [[~~an~~]] the monoclonal antibody of claim 63 ~~any one of claims 63 to 101~~, which comprises,

(i) a step of immunizing an animal with TRAIL-R2 or a fragment thereof, cells expressing the TRAIL-R2 or a fragment thereof ~~having the antigenicity~~, or a DNA containing the gene encoding all or a part of the extracellular domain of TRAIL-R2,

(ii) a step of obtaining monoclonal antibodies from the animal,

(iii) a step of evaluating the activity of the monoclonal antibodies which is a single substance without forming a polymer, binding to TRAIL-R2 and induce apoptosis in carcinoma cells expressing TRAIL-R2, independently of exogenous factors other than the antibody,

(iv) a step of separating the monoclonal ~~a monomer~~ antibody which is a single substance without forming a polymer, and bind to TRAIL-R2 from the antibody,

(v) a step of evaluating the activity of inducing ~~to induce~~ apoptosis of the said monoclonal ~~monomer~~ antibody, and

(vi) a step of selecting the ~~a monomer~~ monoclonal antibody having the activity of inducing ~~to induce~~ apoptosis.

109. (Currently amended) The method of producing [[~~an~~]] the monoclonal antibody of claim 108, wherein step (v) include the following test to determine a survival rate of carcinoma cell using the antibody,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which were colon carcinoma cells, at a concentration of 1.0×10^5/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) [[~~an~~]] the antibody which is bound to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that a concentration of the antibody or the functional fragment thereof becomes 1000ng/ml when it is added to each well at 10μl/well, culturing each well at 37°C under 5.0% carbon dioxide gas for 48 hours, washing each well once with PBS and adding a fresh RPMI-1640 medium containing 10% FCS at100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQ_{UEOUS} Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is calculates using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing carcinoma cells and the antibody or the functional fragment thereof ~~tested~~, "b" represents the measured value of the absorbance of a carcinoma cell-free well, and "c" represents (i) the measured value of the absorbance of a well containing carcinoma cells and a control antibody which is not bound to carcinoma cells and [[~~has~~]] is the same subclass [[with]] as the antibody or the functional fragment thereof bound to TRAIL-R2 when the antibody or the functional fragment thereof has a constant region, or (ii) the measured value of a well containing carcinoma cells and a control antibody which is not bound to the carcinoma cells and does not have a constant region when the antibody or the functional fragment thereof does not have a constant region),

and the antibody having the survival rate of 80% or less is selected.

110. (Currently amended) The method of producing [[~~an~~]] the monoclonal antibody of claim 108, wherein step (v) include the following test to determine a survival rate of carcinoma cell using the antibody,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which were colon carcinoma cells, at a concentration of 1.0 x 10^5/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) [[~~an~~]] the monoclonal antibody which is bound to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that a concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing each well at 37°C under 5.0% carbon dioxide gas for 48 hours, washing each well once with PBS and adding a fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQ$_{UEOUS}$ Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is calculates using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing carcinoma cells and the antibody or the functional fragment thereof ~~tested~~, "b" represents the measured value of the absorbance of a carcinoma cell-free well, and "c" represents the measured value of the absorbance of a well containing carcinoma cells and a control antibody which [[~~has~~]] is the same subclass [[~~with~~]] as the antibody bound to TRAIL-R2 and is not bound to the carcinoma cells),

and the antibody having the survival rate of 80% or less is selected.

111. (Currently amended) The method of producing [[~~an~~]] the monoclonal antibody of claim 108, wherein step (v) include the following test to determine a survival rate of carcinoma cell using the antibody,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which were colon carcinoma cells, at a concentration of 5 x 10^4/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) an antibody which is bound to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that a concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing at 37°C under 5.0% carbon dioxide gas for 1 hour, adding a control antibody which [[~~has~~]] is the same subclass [[~~with~~]] as the antibody bound to TRAIL-R2 and is not bound to carcinoma cells such that a concentration is 100μg/ml, adding goat anti-human IgG (γ)-specific polyclonal antibodies at a final concentration of 10μg/ml, culturing each well at 37°C under 5.0% carbon dioxide gas for 2 days, washing each well once with PBS and adding a fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQ_{UEOUS} Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is calculates using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing carcinoma cells and the antibody or the functional fragment thereof ~~tested~~, "b" represents the measured value of the absorbance of a carcinoma cell-free well, and "c" represents the measured value of the absorbance of a well containing carcinoma cells and a control antibody which [[~~has~~]] is the same subclass [[~~with~~]] as the antibody bound to TRAIL-R2 and is not bound to the carcinoma cells),

and the antibody having the survival rate of 80% or less is selected.

112. (Currently amended) The method of producing [[~~an~~]] the monoclonal antibody of claim 108, wherein step (v) include the following test to determine a survival rate of carcinoma cell using the antibody,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which were colon carcinoma cells, at a concentration of 5 x 10^4/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) [[~~an~~]] the monoclonal antibody which is bound to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that a concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing at 37°C under 5.0% carbon dioxide gas for 1 hour, adding a control antibody which [[~~has~~]] is the same subclass [[~~with~~]] as the antibody bound to TRAIL-R2 and is not bound to carcinoma cell such that a concentration is 3μg/ml, adding goat anti-human IgG (γ)-specific polyclonal antibodies at a final concentration of 10μg/ml, culturing each well at 37°C under 5.0% carbon dioxide gas for 2 days, washing each well once with PBS and adding a fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQ_{UEOUS} Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is calculates using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing carcinoma cells and the antibody or the functional fragment thereof ~~tested~~, "b" represents the measured value of the absorbance of a carcinoma cell-free well, and "c" represents the measured value of the absorbance of a well containing carcinoma cells and a control antibody which [[~~has~~]] is the same subclass [[~~with~~]] as the antibody bound to TRAIL-R2 and is not bound to the carcinoma cells), and the antibody having the survival rate of 80% or less is selected.